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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,546	08/24/2001	Jeffrey Errington	P02186USO	5951

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Patent Department
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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	6

DATE MAILED: 07/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,546	ERRINGTON, JEFFREY	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to the Application and Preliminary Amendment filed May 10, 2001. Claims 1-9, 13 and 14, as filed, and claims 10-12 and 15-19, as amended May 10, 2002, are pending in the application.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not identify the citizenship of each inventor; it does not indicate the status of Application PCT/GB99/03738.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 9-11, 13, and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are drawn to a microorganism in which at least one gene has been partly or wholly replaced by a homologous gene from another microorganism and which contains a reporter gene that is expressed in a manner related to the homologous gene, and methods of using said microorganism to asses inhibitory or antibiotic activities of test compounds. Given the broadest reasonable interpretation according to the definition of homologous in the specification (page 2, lines 11-12), the claimed material encompasses a genus of microorganisms in which one or more genes have been replaced by a functionally equivalent gene, and which also comprises a reporter gene, the expression of which is somehow tied to the expression or activity of the homologous gene or genes. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). The disclosure does provide description of three representative species, which are reduced to practice either in the instant application or in cited work. However, the claimed invention encompasses highly divergent matter (i.e. all recombinant microorganisms, or in some narrower embodiments a recombinant *Bacillus* strain, in which any one gene has been replaced with its functional homologue from any other microorganism alone, or in combination with

replacement of any other gene or multiple genes in the genome of said recombinant microorganism). What is more, the recombinant microorganism must also comprise a reporter gene structured so as to provide a phenotypic indicator of the functional status of the homologous gene or genes. This requirement introduces a high degree of unpredictability, as the means by which expression of the reporter gene is coupled to the status of the homologous gene is highly dependent on which gene or genes are replaced and will, in many cases, have to be determined empirically. For example, in two of the three representative species provided, expression of the reporter gene is coupled to the functional status of the homologous gene as a consequence of a phenotype that arises in *B. subtilis* that does not express a functional *spoIIIE* gene. These species therefore represent only those embodiments of the invention in which activity, or inactivity, of the homologous gene gives rise to the *spoIIIE*-like phenotype. In previous work, Applicant suggests that the number of genes that are tied to a *spoIIIE* phenotype is very limited "As far as we know, no other mutations give rise to a *spoIIIE*-like phenotype" (WO 97/00325). The third representative species provides a means to asses the activity of σ^F or σ^E transcription factors or genes that regulated σ^F or σ^E function, but it does not provide, either alone or in combination with the other representative species, adequate written description of those species wherein the functional status of the homologous gene is not related to σ^F or σ^E function or the *spoIIIE* phenotype.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* embodiments of the invention. Therefore, only the described

embodiments and those embodiments in which the functional status of the homologous gene or genes can be assessed using the reporter constructs of the described embodiments meet the written description provision of 35 U.S.C. §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, and all claims depending from claim 1, are indefinite because, although it would appear that Applicant wishes expression of the reporter gene to be related to the homologous expression product of part (a), use of the indefinite article "a" in referring to the homologous gene in part (b) raises the possibility that the homologous gene of (b) is something different from the gene of (a). Amending claim 1 (b) to read "the homologous gene expression product" would be remedial.

Claim 2 is also indefinite because the antecedent in claim 1 for "the gene" in line 1 could be either the homologous gene of part (a) or the reporter gene of part (b). It would appear that Applicant is referring to the homologous gene and amending the claim to recite "the homologous gene" would be remedial. In addition, the phrase "involved in" in line 1 renders the claim indefinite because it is unclear from the disclosure what constitutes involvement. For example, is a receptor that, when activated, induces synthesis of new proteins involved in protein synthesis? Is a growth factor involved in DNA replication? Or, does involvement limit the scope to direct

participation in the cellular processes of the claim and exclude genes involved in regulation of those processes?

Claim 12 is also indefinite because the term "Spo///E" is not defined in the disclosure. It would appear that Applicant intends that the term be "SpoIIIE" and amending the claim accordingly would be remedial.

Claim 18 is also indefinite because the claim does not recite a preamble. The metes and bounds of the claim are unclear because it is not possible to ascertain whether the final step recited in the claim is truly the terminal step of the claimed invention. Amending the claim to include an appropriate preamble would be remedial.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 9-12 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6 and 9 of U.S. Patent No. 6,027,909 (cited by Applicant in the IDS) in view of Hodgson et al. (U.S. Patent 5,891,667) and in further view of King et al. (WO 92/05244; cited by Applicant in the IDS). Claim 1 of the

instant application is drawn to a microorganism having a chromosome in which: a) at least one gene has been partly or wholly replaced by a homologous gene from another microorganism; and b) an artificially introduced reporter gene that is expressed in a manner related to the homologous gene. Claim 2 limits the [homologous] gene of claim 1 to a gene involved in DNA replication, RNA synthesis, protein synthesis, cell wall synthesis, transport or cell division; Claim 3 limits the microorganism of claim 1 to a bacterium; claim 4 limits the microorganism of claim 3 to a *Bacillus* strain capable of growth and sporulation and in which at least one gene has been replaced by a homologous gene from another bacterium. Claim 5 limits the microorganism of claim 4 to a *Bacillus* strain wherein: a) a *spoIIIE* gene has been replaced by its homologue from another bacterium, and b) two reporter genes are present each linked to a promoter and responsive to σ^F during sporulation, a first reporter gene being located in the segment of DNA trapped in the prespore when SpoIIIE function is impaired, and a second reporter gene being located outside said segment.

Claim 1 of U.S. Patent No. 6,027,909 is drawn to a *Bacillus* strain having a functional SpoIIIE gene, and having a chromosome with first and second reporter genes which reporter genes are different, each reporter gene being linked to a promoter such that said reporter genes are responsive to the action of σ^F during sporulation, said first reporter gene being located in a segment of DNA that is trapped in a prespore compartment when SpoIIIE function is impaired, and said second reporter gene being located outside said segment. The claim is drawn to all of the limitations of claims 1-5 except for the replacement of all or a portion of the SpoIIIE gene with a homologous gene from another microorganism. Hodgson teaches a polynucleotide encoding the SpoIIIE polypeptide from *Staphylococcus aureus* and heterologous

expression of said spoIIIE polypeptide. King teaches replacement of a gene in a microorganism with a homologous gene from another organism. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of claim 1 of U.S. Patent No. 6,027,909 according to the teachings of Hodgson and King to produce the microorganism of claims 1-5. Motivation to combine these teachings comes from Hodgson, who states the usefulness of inhibitors of SpoIIIE function as antibiotics (column 2, lines 24-29) and that, "It is particularly preferred to employ Staphylococcal genes and gene products as targets for the development of antibiotics..." (column 1, lines 16-19); and from Errington (WO 97/00325; 3 January 1997) who states, "The unique sporulation phenotype arising when SpoIIIE is inactivated provides the potential for a very powerful and specific assay" (page 2, lines 23-25). One would have a reasonable expectation of success in combining these teachings because, as Hodgson teaches, the high degree of conservation among SpoIIIE homologues of diverse bacterial species "strongly suggests commonality of function" and thus a reasonable expectation that heterologous expression of the SpoIIIE gene from one microorganism will complement inactivation of the SpoIIIE gene of the recombinant microorganism.

Claim 9 of the instant application limits the *Bacillus* strain of any one of claims 4-8 to a *B. subtilis* strain. Claim 5 of U.S. Patent No. 6,027,909 limits the *Bacillus* strain of claim 1 to a *B. subtilis* strain. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of the claim according to the teachings of Hodgson and King to produce the microorganism of claim 9 of the instant application. One would be motivated to combine these teachings and would have a reasonable expectation of success for the reasons provided above.

Claim 10 of the instant application is drawn to a method of assessing an agent for antibiotic activity comprising steps of a) incubating the microorganism of claim 1 in the presence of the agent, and b) observing expression of the reporter gene or genes. Claim 11 limits the microorganism of claim 10 to a *Bacillus* strain as defined in claim 4 and is induced to sporulate in the presence of the agent. Claim 12 is drawn to a method of determining whether an agent inhibits [SpoIIIE] function in a *Bacillus* species comprising inducing the *Bacillus* strain of claim 5 to sporulate in the presence of the agent, and observing expression of the first and the second reporter genes; and claim 18 is drawn to a method which comprises incubating the microorganism of claim 1 in the presence of an agent, observing expression of one or more reporter genes, thereby determining that the agent inhibits growth of the microorganisms, and using the agent as an antibiotic.

Claim 9 of U.S. Patent No. 6,027,909 is drawn to a method which comprises inducing the *Bacillus* strain of claims 1 or 5 to sporulate in the presence of an agent, observing expression of the first and second reporter genes and thereby determining that the agent inhibits SpoIIIE function in the *Bacillus* species, and using the agent as an antimicrobial agent to kill or control the growth of bacteria. The claim is drawn to each of the limitations of claims 10-12 and 18 except for the replacement of all or a portion of the SpoIIIE gene with a homologous gene from another microorganism. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of the claim according to the teachings of Hodgson and King as described above to produce the methods of claims 9-12 and 18 of the instant application. One would be motivated to combine these teachings and would have a reasonable expectation of success for the reasons provided above.

Claims 1, 3, 4, 8 and 14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,350,587 (cited by Applicant in the IDS as U.S. Patent Application No. 09/319,777) in view of Jaworski et al. (U.S. Patent No. 6,080,729) and in further view of King.

The limitations of claims 1, 3 and 4 are recited above. Claim 8 limits the microorganism of claim 4 to a *Bacillus* strain wherein: a) a spo*OJ* gene has been replaced by its homologue from another bacterium, and b) one or two reporter genes are present, a first reporter gene having a promoter which is dependent on σ^F factor and placed at a location where impaired Spo*OJ* function leads to increased trapping and hence to increased expression in the prespore, and/or a second reporter gene having a promoter which is dependent on σ^F and placed in a location where impaired Spo*OJ* function leads to reduced trapping and hence to reduced expression. Claim 14 is drawn to a method of determining whether an agent inhibits Spo*OJ* function in *Bacillus* species, which method comprises inducing the *Bacillus* strain of claim 8 to divide asymmetrically in the presence of an agent, and observing expression of the first and/or second reporter genes.

Claim 1 of U.S. Patent No. 6,350,587 is drawn to a method of determining whether an agent inhibits Spo*OJ* function in *Bacillus* species comprising: providing a *Bacillus* strain having a functional Spo*OJ* gene and having a chromosome with the following modifications; a) a mutation of a spo*IIIE* gene which blocks transfer of the prespore chromosome, b) a mutation of fsoj which prevents loss of Spo*OJ* function from blocking sporulation, together with, c) a first reporter gene having a promoter which is dependent on σ^F factor and placed at a location on said chromosome where impaired Spo*OJ* function leads to increased trapping of said first reporter

gene..., and/or d) a second reporter gene having a promoter which is dependent on σ^F factor and placed at a location on said chromosome where impaired Spo*OJ* function leads to reduced trapping of said second reporter gene..., inducing said *Bacillus* strain to divide asymmetrically in the presence of the agent and observing expression of the first and/or the second reporter gene. The claim is drawn to all of the limitations of claims 1, 3, 4, 8 and 14 of the instant application except for the replacement of all or a portion of the Spo*OJ* gene with a homologous gene from another microorganism. Jaworski teaches a polynucleotide encoding the spo*OJ* polypeptide from *Staphylococcus aureus* and heterologous expression of said spo*OJ* polypeptide. As described above, King teaches replacement of a gene in a microorganism with a homologous gene from another organism. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of claim 1 of U.S. Patent No. 6,350,587 according to the teachings of Jaworski and King to produce the microorganism and methods of claims 1, 3, 4, 8 and 14 of the instant application. Motivation to combine these teachings and a reasonable expectation of success can again be found in the teachings of Hodgson regarding the preferability of employing Staphylococcal genes and gene products as targets for antibiotics, and in the teachings of Errington regarding the powerful and specific nature of the Spo*IIIE* phenotype as an assay. One would have a reasonable expectation of success in combining these teachings in view of Jaworski who teaches that the disclosed polypeptides possess amino acid homology to a known *B. subtilis* protein similar to DNA binding protein spo*OJ* (column 1, lines 46-49).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim19 rejected under 35 U.S.C. 102(b) as being anticipated by Düwel et al. (1975; U.S. Patent No. 3,888,978). The claim is drawn to a method of killing or inhibiting the growth of bacteria comprising contacting the bacteria with an agent which inhibits the growth of a microorganism of claim 1. It should be noted that the claim is not limited to an agent that inhibits the growth of the microorganism of claim 1 by acting on the product of the homologous gene. Therefore any compound capable of killing or inhibiting a microorganism anticipates the claim. Düwel teaches a method of killing or inhibiting the growth of microorganisms using phosphorus acid esters, which meets the limitations of the claim.

What is more, there is insufficient written description in the disclosure to support a claim in which the scope is narrowed to comprise only those compounds that inhibit the growth of the microorganism of claim 1 by acting on the product of the homologous gene. Such a claim would require disclosure of a means to distinguish those compounds from compounds that act elsewhere.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 9-12, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Errington (1997; WO 97/00325; cited by Applicant in the IDS) in view of Hodgson and in further view of King as applied to the claims under the doctrine of obviousness-type double-patenting above. The disclosure of Errington is the same as for U.S. Patent No. 5,891,667, therefore the reasoning behind this rejection is the same as the double-patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
June 28, 2002

JAMES KETTER
PRIMARY EXAMINER